#3

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Seini Matangi
(Typed or printed name of person mailing paper or fee)

(Signature of person mailing paper or fee)

Patent
Attorney Docket No. 018413-257

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	)	
	)	
Thomas WHALEN, et al.	)	
	)	Group Art Unit: Unassigned
Application No.: 09/574,379	)	
	)	Examiner: Unassigned
Filed: May 19, 2000	)	
	)	
For: NOVEL HIGH VISCOSITY EMBOLIZING COMPOSITIONS	)	

PETITION UNDER 37 C.F.R.§1.47(a) WHEN INVENTORS REFUSE TO SIGN OR CANNOT BE LOCATED

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This petition is submitted pursuant 37 C.F.R. §1.47(a) and MPEP §409.03 in order to have this application accepted as complete and proceed to examination not withstanding the lack of a signed Declaration from all of the inventors.

Specifically, Petitioner notes that a Notice of Missing Parts of Application was mailed by the United States Patent and Trademark Office (the "Patent Office") on July 27, 2000. A response to that Notice and a Petition requesting a five-month extension of time to respond to the Notice are submitted concurrently. This Petition is submitted to have the application accepted since, after diligent effort, one inventor has failed to return or refuses to execute the required Declaration.

EXHIBIT 1

Pursuant to MPEP §409.03(a)(A), this Petition is accompanied by a Combined Declaration and Power of Attorney which has been executed by the available signing inventors Thomas J. Whalen ("Inventor Whalen"), Noah M. Roth ("Inventor Roth") and Richard J. Greff ("Inventor Greff") and the fee required under 37 C.F.R. §1.17(i). Inventor Chinh N. Tran ("Inventor Tran") refuses to execute the required Declaration.

FACTS

Inventors Whalen, Roth and Greff

As noted above, inventors Thomas J. Whalen, Noah M. Roth and Richard J. Greff have executed a Declaration which is enclosed herewith. As required by MPEP §409.03(a)(A), all of the available joint inventors have (1) made an oath or declaration on their own behalf and (2) made the oath or declaration on behalf of the non-signing joint inventors. The proof that the non-signing inventor refuses to execute the application papers pursuant to MPEP §409.03(a)(B) and MPEP §409.03(d) is set forth below, together with his last known address, as required by MPEP §409.03(a)(C).

Inventor Chinh N. Tran

Mr. Earl H. Slee, Vice President of Research and Development at Micro Therapeutics, Inc. ("MTI"), has spoken to Mr. Tran on numerous occasions asking Mr. Tran to sign the assignment for the required Declaration. See, Declaration of Slee, attached as Exhibit A. Mr. Tran has consistently refused to sign the required Declaration because his name is not placed first among the list of inventors. Id.

Ms. Rebecca M. Hale, an associate at Burns, Doane, Swecker and Mathis, a law firm representing MTI, sent a copy of the Application and Declaration to inventor Tran at his last known address, 21741 Alvarez, Mission Viejo, California 92691 via Certified Mail, Return of Receipt Requested on January 31, 2001. A copy of the letter and its attachments is attached as Exhibit B. This letter also included an Assignment document and a copy of Mr. Tran's employment agreement relating to Mr. Tran's obligations to assign inventions made or conceived by him during his employment at MTI and to assist MTI to obtain patents for the assigned inventions, during and at any time subsequent to his employment.

Mr. Tran signed for the receipt of the letter on February 2, 2001, as demonstrated by the returned Receipt postcard. A pre-paid United States Express Mail return envelope was also enclosed in the package for Mr. Tran's convenience. The letter stated that if Mr. Tran did not return the signed document to Ms. Hale by February 23, 2001, MTI would file a petition to proceed with the prosecution of the application on his behalf.

Mr. Tran called Ms. Hale on February 21, 2001 and said that he would not sign the declaration because he did not agree with the order the inventors were listed on the declaration. See, Declaration of Hale, attached as Exhibit C. After Ms. Hale told Mr. Tran that the order of the inventors would not be changed, he asked to speak to a more senior attorney at Ms. Hale's lawfirm. Id.

Ms. Hale and Ms. Mary Ann Dillahunty, a partner at Burns, Doane, Swecker and Mathis, spoke to Mr. Tran by telephone on Feburary 26, 2001. Id. During this conversation, Ms. Dillahunty explained to Mr. Tran that, while it was important to ensure that the correct inventors were listed in the patent application, there was no legal error in the current order of the inventors. Id. Ms. Dillahunty reiterated that, pursuant to instructions of MTI, the order of inventors would not be changed. Id. Mr. Tran did not dispute that the correct inventors were listed in the declaration, but he said that he was currently unwilling to sign the declaration because his name was not listed first. Id. Ms. Dillahunty and Ms. Hale told Mr. Tran that, given his refusal to sign the required Declaration, MTI would proceed with a petition to complete the application without his signature. Id.

Last Known Address of Nonsigning Joint Inventor

The last known address of Mr. Tran is:

Mr. Chinh Tran
21741 Alvarez
Mission Viejo, California 92691

Requested Relief

Petitioners respectfully request that this application be accepted under 37 C.F.R. §1.47(a) without the executed Declaration of Inventor Tran. As noted above, after he was presented with a copy of the application, Inventor Tran refused to execute the Declaration for submission to the Patent Office. Accordingly, Petitioners submit that they have complied with the requirements of 37 C.F.R. §1.47 and MPEP §409.03, and request that this application proceed to examination.

Respectfully submitted,
BURNS, DOANE, SWECKER & MATHIS, LLP

By: Rebecca M. Hale

Rebecca M. Hale
Reg. No.45,680
Attorney for Applicants
Redwood Shores, CA Office
(650) 622-2324

P.O. Box 1404
Alexandria, Virginia 22313-1404

February 27, 2001

EXHIBIT A

Patent
Attorney's Docket No. 018413-257

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of	
Thomas WHALEN, et al.	Group Art Unit: Unassigned
Application No.: 09/574,379	Examiner: Unassigned
Filed: May 19, 2000	
For: NOVEL HIGH VISCOSITY EMBOLIZING COMPOSITIONS	

DECLARATION OF EARL H. SLEE
IN SUPPORT OF PETITION UNDER 37 C.F.R.§1.47(a)
WHEN INVENTORS REFUSE TO SIGN OR CANNOT BE LOCATED

Assistant Commissioner for Patents
Washington, D.C. 20231

I, Earl H. Slee, hereby declare:

1. I am currently employed at Micro Therapeutics, Inc. ("MTI") as Vice President of Research and Development. I have been employed at MTI since April 6, 1998.

2. As part of my responsibilities at MTI, I supervise the filing and prosecution of patent applications, including U.S. Patent Application Serial No. 09/574,379 ("the '379 Application"). Mr. Chinh Tran was identified by MTI as an inventor of the '379 Application.

3. On several occasions, I spoke with Mr. Tran regarding his refusal to sign the Declaration and Assignment for the '379 Application. He consistently refused to sign these documents because he was not listed as the first inventor.

EXHIBIT A

Patent
Attorney's Docket No. 018413-257

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Signed: _____ Dated: _____

EXHIBIT A

Patent

Attorney's Docket No. 018413-257

4. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application of any patent issued thereon.

Signed: Earl Hall Dated: 2/27/01

EXHIBIT B

SENDER: COMPLETE THIS SECTION

- Complete items 1, 2, and 3. Also complete item 4 if Restricted Delivery is desired.
- Print your name and address on the reverse so that we can return the card to you.
- Attach this card to the back of the mailpiece, or on the front if space permits.

1. Article Addressed to:

Mr. Chinh Tran
21741 Alvarez
Mission Viejo, CA
92691

COMPLETE THIS SECTION ON DELIVERY

A. Received by *(Please Print Clearly)* | B. Date of Delivery 2/2/01

C. Signature
X [signature] ☐ Agent ☐ Addressee

D. Is delivery address different from item 1? ☐ Yes
If YES, enter delivery address below: ☐ No

3. Service Type
☒ Certified Mail ☐ Express Mail
☐ Registered ☐ Return Receipt for Merchandise
☐ Insured Mail ☐ C.O.D.

4. Restricted Delivery? *(Extra Fee)* ☐ Yes

2. Article Number *(Copy from service label)*
7000 1670 0013 1666 0321

PS Form 3811, July 1999 Domestic Return Receipt 102595-00-M-0952

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Return Receipt Fee (Endorsement Required)	1.50
Restricted Delivery Fee (Endorsement Required)	
Total Postage & Fees	$ 5.84

SAN FRANCISCO, CA AIRPORT BR JAN 31 2001 Postmark Here USPS

Sent To Mr. Chinh Tran
Street, Apt. No., or PO Box No. 21741 Alvarez
City, State, ZIP+4 Mission Viejo, CA 92691

PS Form 3800, May 2000 See Reverse for Instructions

7000 1670 0013 1666 0321

BURNS DOANE

BURNS DOANE SWECKER & MATHIS LLP

ALEXANDRIA, VIRGINIA
REDWOOD SHORES, CALIFORNIA
DURHAM, NORTH CAROLINA

Office Address:
Suite 700
333 Twin Dolphin Drive
Redwood Shores, California 94065-1418

Telephone: +1.650.622.2300
Fax: +1.650.622.2499

January 30, 2001

REBECCA M. HALE
E-MAIL - REBECCAH@BURNSDOANE.COM
TELEPHONE: +1.650.622.2335

FILE COPY

VIA CERTIFIED MAIL

Mr. Chinh Tran
21741 Alvarez
Mission Viejo, California 92691

Re: Declaration and Assignment for U.S. Patent Application Serial No. 09/574,379
For: NOVEL HIGH VISCOSITY EMBOLIZING COMPOSITIONS
Filed: May 19, 2000

Dear Mr. Tran:

We represent Micro Therapeutics, Inc. ("MTI") in the patent prosecution of the above-identified United States patent application ("the '379 Application"). We understand that you are a joint inventor for the invention claimed in the '379 Application. Based on our conversations with Earl H. Slee, Vice President of Research and Development at MTI, we understand that you have refused to sign the declaration and assignment for the '379 Application.

Notwithstanding the above, enclosed please find an execution copy of the declaration and assignment for your signature along with a copy of the '379 Application as filed with the U.S. Patent and Trademark Office ("USPTO"). In addition we enclose a copy of your employment agreement with MTI, signed by you on October 1, 1998. We note that paragraph 4 relates to your assignment of inventions made or conceived by you during the period of your employment with MTI. Paragraph 5(b) relates further to your assignment obligations. Paragraph 5(c) relates to your agreement to assist MTI "during and at any time subsequent" to your employment to obtain patents for the assigned inventions.

If you refuse to sign the assignment and declaration, please check the appropriate box below and return it to me using the addressed, postage paid Express Mail package enclosed. Please note that upon your refusal to sign, MTI reserves the legal right to pursue prosecution of this application on your behalf. MTI also reserves the right to file a copy of your employment agreement with the Assignment division of the USPTO to give public notice of your obligation to assign this patent application to MTI.

If you have any questions regarding your obligations to sign the assignment or declaration papers, we strongly encourage you to seek you own, independent legal counsel. As stated above, we represent MTI in the prosecution of the '379 Application. We are not and can not offer you any legal advice regarding this matter. Should you decide to sign the declaration and assignment, I must receive it by no later than **February 23, 2001** in order to avoid filing the above mentioned petition.

Thank you for your courtesy and cooperation.

Sincerely,

Rebecca M. Hale

Rebecca M. Hale

Enclosures
cc: Earl H. Slee (w/ encls.)
Robert E. Krebs (w/o encls.)
Gerald F. Swiss (w/o encls.)

U.S. Patent Application Serial No. 09/574,379
BDSM RN 018413-257

_____ I, Chinh Tran, refuse to sign the declaration and assignment papers for U.S. Patent Application Serial No. 09/574,379. I understand that MTI reserves the legal right to pursue prosecution of this application on my behalf, notwithstanding my refusal. I further understand that MTI reserves the right to file a copy of my employment agreement with the Assignment division of the U.S. Patent and Trademark Office to give public notice of my obligation to assign this patent application to MTI.

_____ _____
(signed) (dated)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (Includes Reference to Provisional and PCT International Applications)	Attorney's Docket No. 018413-257

As a below named inventor, I hereby declare that:
My residence, post office address and citizenship are as stated below next to my name;
I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

NOVEL HIGH VISCOSITY EMBOLIZING COMPOSITIONS

the specification of which (check only one item below):

☐ is attached hereto.

☒ was filed as United States application
Number 09/574,379
on May 19, 2000
and was amended
on _____ (if applicable).

☐ was filed as PCT international application
Number _____
on _____
and was amended
on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(e) of any foreign application(s) for patent or inventor's certificate or of any PCT international application(s) designating at least one country other than the United States of America listed below and have also identified below any foreign application(s) for patent or inventor's certificate or any PCT international application(s) designating at least one country other than the United States of America filed by me on the same subject matter having a filing date before that of the application(s) of which priority is claimed:

PRIOR FOREIGN/PCT APPLICATION(S) AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. §119:

COUNTRY (if PCT, indicate "PCT")	APPLICATION NUMBER	DATE OF FILING (day, month, year)	PRIORITY CLAIMED UNDER 35 U.S.C. §119
			_ Yes _ No
			_ Yes _ No
			_ Yes _ No
			_ Yes _ No
			_ Yes _ No

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

60/135,288	May 21, 1999
(Application Number)	(Filing Date)
_____	_____
(Application Number)	(Filing Date)

(1/00)

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D) (Includes Reference to Provisional and PCT International Applications)	Attorney's Docket No. 018413-257

I hereby claim the benefit under Title 35, United States Code, §120 of any United States applications(s) or PCT international application(s) designating the United States of America that is/are listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in that/those prior application(s) in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose to the Office all information known to me to be material to the patentability as defined in Title 37, Code of Federal Regulations §1.56, which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. APPLICATIONS OR PCT INTERNATIONAL APPLICATIONS DESIGNATING THE U.S. FOR BENEFIT UNDER 35 U.S.C. §120:

U.S. APPLICATIONS		STATUS *(check one)*		
U.S. APPLICATION NUMBER	U.S. FILING DATE	PATENTED	PENDING	ABANDONED

PCT APPLICATIONS DESIGNATING THE U.S.					
PCT APPLICATION NO.	PCT FILING DATE	U.S. APPLICATION NUMBERS ASSIGNED (if any)			

I hereby appoint the following attorneys and agent(s) to prosecute said application and to transact all business in the Patent and Trademark Office connected therewith and to file, prosecute and to transact all business in connection with international applications directed to said invention:

William L. Mathis	17,337	R. Danny Huntington	27,903	Gerald F. Swiss	30,113
Robert S. Swecker	19,885	Eric H. Weisblatt	30,505	Michael J. Ure	33,089
Platon N. Mandros	22,124	James W. Peterson	26,057	Charles F. Wieland III	33,096
Benton S. Duffett, Jr.	22,030	Teresa Stanek Rea	30,427	Bruce T. Wieder	33,815
Norman H. Stepno	22,716	Robert E. Krebs	25,885	Todd R. Walters	34,040
Ronald L. Grudziecki	24,970	William C. Rowland	30,888	Ronni S. Jillions	31,979
Frederick G. Michaud, Jr.	26,003	T. Gene Dillahunty	25,423	Harold R. Brown III	36,341
Alan E. Kopecki	25,813	Patrick C. Keane	32,858	Allen R. Baum	36,086
Regis E. Slutter	26,999	Bruce J. Boggs, Jr.	32,344	Steven M. du Bois	35,023
Samuel C. Miller, III	27,360	William H. Benz	25,952	Brian P. O'Shaughnessy	32,747
Robert G. Mukai	28,531	Peter K. Skiff	31,917	Kenneth B. Leffler	36,075
George A. Hovanec, Jr.	28,223	Richard J. McGrath	29,195	Fred W. Hathaway	32,236
James A. LaBarre	28,632	Matthew L. Schneider	32,814		
E. Joseph Gess	28,510	Michael G. Savage	32,596		

21839

and: Leslie J. Boley, Reg. No. 41,490; Rekha Bansal, Reg. No. 36,440; Ping Hwung, Reg. No. 44,164, and Rebecca Hale, Reg. No. 45,680.

Address all correspondence to:

21839

Robert E. Krebs, Esq.
BURNS, DOANE, SWECKER & MATHIS, L.L.P.
P.O. Box 1404
Alexandria, Virginia 22313-1404

Address all telephone calls to: Gerald F. Swiss, Esq. at (650) 622-2300.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

COMBINED DECLARATION FOR PATENT APPLICATION AND POWER OF ATTORNEY (CONT'D) (Includes Reference to Provisional and PCT International Applications)	Attorney's Docket No. 018413-257

FULL NAME OF SOLE OR FIRST INVENTOR Thomas J. Whalen	SIGNATURE	DATE
RESIDENCE 720 Fieldstone Lane, Encinitas, California 92024	CITIZENSHIP US	
POST OFFICE ADDRESS 720 Fieldstone Lane, Encinitas, California 92024		
FULL NAME OF SECOND JOINT INVENTOR, IF ANY Chinh N. Tran	SIGNATURE	DATE
RESIDENCE 21741 Alvarez, Mission Viejo, California 92691	CITIZENSHIP US	
POST OFFICE ADDRESS 21741 Alvarez, Mission Viejo, California 92691		
FULL NAME OF THIRD JOINT INVENTOR, IF ANY Noah M. Roth	SIGNATURE	DATE
RESIDENCE 203 Esplanade, Irvine, California 92612	CITIZENSHIP US	
POST OFFICE ADDRESS 203 Esplanade, Irvine, California 92612		
FULL NAME OF FOURTH JOINT INVENTOR, IF ANY Richard J. Greff	SIGNATURE	DATE
RESIDENCE 2891 Alton Drive, St. Pete Beach, Florida 33706	CITIZENSHIP US	
POST OFFICE ADDRESS 2891 Alton Drive, St. Pete Beach, Florida 33706		
FULL NAME OF FIFTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF SIXTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF SEVENTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		
FULL NAME OF EIGHTH JOINT INVENTOR, IF ANY	SIGNATURE	DATE
RESIDENCE	CITIZENSHIP	
POST OFFICE ADDRESS		

018413-257
Attorney's Docket No.

ASSIGNMENT

(JOINT)

THIS ASSIGNMENT, by THOMAS J. WHALEN, CHINH N. TRAN, NOAH M. ROTH, and RICHARD J. GREFF, residing at 720 FIELDSTONE LANE, ENCINITAS, CA. 92024, 21741 ALVAREZ, MISSION VIEJO, CA. 92691, 203 ESPLANADE, IRVINE, CA. 92612 and 2891 ALTON DR., ST. PETE BEACH, FL. 33706 (hereinafter referred to as "the Assignors"), respectively, witnesseth:

WHEREAS, the Assignors have invented certain new and useful improvements in NOVEL HIGH VISCOSITY EMBOLIZING COMPOSITIONS set forth in an application for Letters Patent of the United States,

(1) ☐ which is a provisional application
  (a) ☐ to be filed herewith; or
  (b) ☐ bearing Application No. , and filed on ; or

(2) ☒ which is a non-provisional application
  (a) ☐ having an oath or declaration executed on even date herewith prior to filing of application;
  (b) ☒ bearing Application No. 09/574,379, and filed on MAY 19, 2000; or
  (c) ☐ to be filed; and

WHEREAS, MICROTHERAPEUTICS, INC., a corporation duly organized under and pursuant to the laws of CALIFORNIA and having its principal place of business at 2 GOODYEAR DRIVE, IRVINE, CA 92618 (hereinafter referred to as "the Assignee"), is desirous of acquiring the entire right, title, and interest in and to said inventions, the right to file applications on said inventions and the entire right, title and interest in and to any applications, including provisional applications for Letters Patent of the United States or other countries claiming priority to said application, and in and to any Letters Patent or Patents, United States or foreign, to be obtained therefor and thereon.

NOW, THEREFORE, in consideration of One Dollar ($1.00) and other good and sufficient consideration, the receipt of which is hereby acknowledged, the Assignors have sold, assigned, transferred, and set over, and by these presents do sell, assign, transfer, and set over, unto the Assignee, its successors, legal representatives, and assigns the entire right, title, and interest in and to the above-mentioned inventions, the right to file applications on said inventions and the entire right, title and interest in and to any applications for Letters Patent of the United States or other countries claiming priority to said applications, and any and all Letters Patent or Patents of the United States of America and all foreign countries that may be granted therefor and thereon, and in and to any and all applications claiming priority to said applications, divisions, continuations, and continuations-in-part of said applications, and reissues and extensions of said Letters Patent or Patents, and all rights under the International Convention for the Protection of Industrial Property, the same to be held and enjoyed by the Assignee, for its own use and behalf and the use and behalf of its successors, legal representatives, and assigns, to the full end of the term or terms for which Letters Patent or Patents may be granted as fully and entirely as the same would have been held and enjoyed by the Assignors had this sale and assignment not been made;

AND for the same consideration, the Assignors hereby covenant and agree to and with the Assignee, its successors, legal representatives, and assigns, that, at the time of execution and delivery of these presents, the Assignors are the sole and lawful owners of the entire right, title, and interest in and to the inventions set forth in said applications and said applications, including provisional applications, above-mentioned, and that the same are unencumbered, and that the Assignors have good and full right and lawful authority to sell and convey the same in the manner herein set forth;

AND for the same consideration, the Assignors hereby covenant and agree to and with the Assignee, its successors, legal representatives, and assigns that the Assignors will, whenever counsel of the Assignee, or the counsel of its successors, legal representatives, and assigns, shall advise that any proceeding in connection with said inventions or said applications for Letters Patent or Patents, or any proceeding in connection with Letters Patent or Patents for said inventions in any country, including interference proceedings, is lawful and desirable, or that any application claiming priority to said application, division, continuation, or continuation-in-part of any applications for Letters Patent or Patents, or any reissue or extension of any Letters Patent or Patents to be obtained thereon, is lawful and desirable, sign all papers and documents, take all lawful oaths, and do all acts necessary or required to be done for the procurement, maintenance, enforcement, and defense of Letters Patent or Patents for said inventions, without charge to the Assignee, its successors, legal representatives, and assigns, but at the cost and expense of the Assignee, its successors, legal representatives, and assigns;

AND the Assignors hereby authorize and request the attorneys of BURNS, DOANE, SWECKER & MATHIS, L.L.P. of Alexandria, Virginia to insert in the spaces provided above the filing date, application number, and attorney docket number of said application when known.

AND the Assignors hereby request the Commissioner of Patents to issue any and all said Letters Patent of the United States to the Assignee as the Assignee of said inventions, the Letters Patent to be issued for the sole use and behalf of the Assignee, its successors, legal representatives, and assigns.

Date_____ Signature of Assignor _____
Thomas J. Whalen

Date_____ Signature of Assignor _____
Chinh N. Tran

Date_____ Signature of Assignor _____
Noah M. Roth

Date_____ Signature of Assignor _____
Richard J. Greff

"Express Mail" mailing label No. EL521770382US
Date of Deposit May 19, 2000
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to BOX PATENT APPLICATION, Assistant Commissioner for Patents, Washington, D.C. 20231.
Nanci MacArthur
(Typed or printed name of person mailing paper or fee)
Nanci MacArthur
(Signature of person mailing paper or fee)

PATENT
Attorney Docket No. 018413-257

BE IT KNOWN that WE, Thomas J. Whalen, Chinh N. Tran, Noah M. Roth and Richard J. Greff have invented new and useful improvements in

NOVEL HIGH VISCOSITY EMBOLIZING COMPOSITIONS

NOVEL HIGH VISCOSITY EMBOLIZING COMPOSITIONS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 60/135,288, filed May 21, 1999 which application is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

Field of the Invention

This invention is directed to novel compositions for embolizing blood vessels which are particularly suited for treating aneurysms, arteriovenous malformations (AVMs) at high flow fistulas and embolizing blood vessels.

In one embodiment, the compositions of this invention comprise a biocompatible polymer, a biocompatible solvent and a biocompatible contrast agent wherein the viscosity of the composition is at least about 150 cSt and preferably at least about 200 cSt at 40°C.

References

The following publications are cited in this application as superscript numbers:

[1] Mandai, et al., "Direct Thrombosis of Aneurysms with Cellulose Acetate Polymer", *J. Neurosurg.*, 77:497-500 (1992)

[2] Kinugasa, et al., "Direct Thrombosis of Aneurysms with Cellulose Acetate Polymer", *J. Neurosurg.*, 77:501-507 (1992)

[3] Casarett and Doull's *Toxicology*, Amdur et al., Editors, Pergamon Press, New York, pp. 661-664 (1975)

[4] Greff, et al., *U.S. Patent No.5,667,767* for "Novel Compositions for Use in Embolizing Blood Vessels", issued on September 16, 1997

[5] Greff, et al., *U.S. Patent No. 5,580,568* for "Cellulose Diacetate Compositions for Use in Embolizing Blood Vessels", issued on December 3, 1996

[6] Kinugasa, et al., "Early Treatment of Subarachnoid Hemorrhage After Preventing Rerupture of an Aneurysm", *J. Neurosurg.*, 83:34-41 (1995)

[7] Kinugasa, et al., "Prophylactic Thrombosis to Prevent New Bleeding and to Delay Aneurysm Surgery", *Neurosurg.*, 36:661 (1995)

[8] Taki, et al., "Selection and Combination of Various Endovascular Techniques in the Treatment of Giant Aneurysms", *J. Neurosurg.*, 77:37-42 (1992)

[9] Evans, et al., *U.S. Patent Application Serial No. 08/655,822* for "Novel Compositions for Use in Embolizing Blood Vessels", filed May 31, 1996.

[10] Dunn, et al., *U.S. Patent No. 4,938,763* for "*Biodegradable In-Situ Forming Implants and Methods of Producing Same*", issued July 3, 1990

All of the above references are herein incorporated by reference in their entirety to the same extent as if each individual reference was specifically and individually indicated to be incorporated herein by reference in its entirety.

State of the Art

Embolization of blood vessels is conducted for a variety of purposes including the treatment of tumors, the treatment of lesions such as aneurysms, uncontrolled bleeding and the like.

Embolization of blood vessels is preferably accomplished via catheter techniques which permit the selective placement of the catheter at the vascular site to be embolized. In this regard, recent advancements in catheter technology as well as in angiography now permit neuroendovascular intervention including the treatment of otherwise inoperable lesions. Specifically, development of microcatheters and guide wires capable of providing access to vessels as small as 1 mm in diameter allows for the endovascular treatment of many lesions.

Embolizing compositions (embolic compositions) heretofore disclosed in the art include those comprising a biocompatible polymer, a biocompatible solvent and a contrast agent which allowed visualization of the *in vivo* delivery of the composition via fluoroscopy.[1-8] Such compositions typically contain no more than about 8 weight percent of biocompatible polymer based on the weight of the total composition.

Notwithstanding the benefits associated with the use of such embolic compositions in treating aneurysms and other vascular disorders, *in vivo* these compositions formed coherent masses which often suffer from solidification and formation of a coherent mass distal from the point of ejection from the catheter. That is to say that upon ejection of the embolic composition in a vascular site, the coherent mass subsequently formed was often distal and not proximate the ejection port of the catheter. Moreover, upon solidification, the solid mass formed was often linear in shape (i.e., having a "string shape").

In many circumstances, a contiguous or ball shape precipitate formed at the ejection port is desired (e.g., to fill an aneurysm). Distal solidification of a string shape precipitate makes site specific delivery of the solid mass in the vasculature difficult. As is apparent, site specific delivery of the solid mass is essential for treatment of vascular disorders such as aneurysms. Solidification at points distal to the ejection port, as is common in string shape precipitates, can result in the solid mass forming not in the aneurysm sac but in the artery attendant the aneurysm. Such a string shape precipitate is more prone to fragmentation which can lead to embolization of this artery and possible incapacitation or death of the patient. Moreover, such fragmentation can lead to particles or fragments being "washed" downstream and lodging at undesired locations in the vasculature.

This invention is based, in part, on the discovery that the formation of a solid non-migratory mass having a substantially contiguous or "ball" shape can be achieved by use of embolic compositions comprising a biocompatible polymer, a biocompatible solvent and optionally a contrast agent wherein the composition has a viscosity of at least about 150 cSt at 40°C. The use of such high viscosity embolic compositions was heretofore not preferred in view of

the fact that the viscosity of these compositions is significantly higher than those containing 8 weight percent polymer thereby rendering it difficult to employ conventional delivery means (e.g., syringe) for use in combination with the catheter for the controlled delivery of these compositions *in vivo*.

However, delivery means such as the threaded syringes described, for example, in U.S. Provisional Patent Application Serial Nos. 60/135,289 and 60/135,287, entitled "THREADED SYRINGE" under Attorney Docket No. 018413-194 and entitled "SCREW SYRINGE WITH FORCE RELEASE MECHANISM" under Attorney Docket No. 018413-198, both of which were filed on May 21, 1999, now renders the use of these highly viscous compositions practical. Both of these applications are incorporated herein by reference in their entirety.

SUMMARY OF THE INVENTION

This invention is directed to the novel and unexpected discovery that the use of embolic compositions comprising a viscosity of at least about 150 cSt at 40°C provides for the *in vivo* formation of a solid, non-migratory mass which mass is substantially contiguous in shape.

Without being limited to any theory, it is now believed that embolic compositions having such a high viscosity permit more rapid and consistent solidification *in vivo* thereby rendering the solid mass formed non-migratory and substantially contiguous in shape. It is further believed that the rapid and consistent solidification *in vivo* arises at least in part from the high viscosity of these compositions which renders migration from the ejection port of the catheter at the vascular site more difficult.

Accordingly, in one of its composition aspects, this invention is directed to a composition comprising a biocompatible polymer, a biocompatible contrast agent, and a biocompatible solvent which solubilizes said biocompatible polymer

wherein sufficient amounts of said polymer are employed in said composition such that, upon delivery to a vascular site, a polymer precipitate forms which embolizes said vasculare site; and

further wherein the viscosity of said composition is at least about 150 cSt at 40°C.

In another of its composition aspects, this invention is directed to a composition comprising:

(a) a biocompatible polymer at a concentration of from about 2 to 50 weight percent;

(b) a biocompatible contrast agent at a concentration of from about 10 to about 40 weight percent; and

(c) a biocompatible solvent from about 10 to 88 weight percent

wherein the weight percent of the biocompatible polymer, contrast agent and biocompatible solvent is based on the total weight of the complete composition; and

further wherein the composition has a viscosity of at least about 150 and more preferably at least about 200 cSt at 40°C.

Preferably in this particular composition, the concentration of the polymer ranges from 6 to 50 weight percent and more preferably 8 to 30 weight percent.

In another of its composition aspects, this invention is directed to a composition comprising:

(a) a biocompatible polymer at a concentration of from about 12 to 50 weight percent;

(b) a biocompatible contrast agent at a concentration of from about 10 to about 40 weight percent; and

(c) a biocompatible solvent from about 10 to 78 weight percent

wherein the weight percent of the biocompatible polymer, contrast agent and biocompatible solvent is based on the total weight of the complete composition and

further wherein the composition has a viscosity of at least about 150, preferably at least about 200 and more preferably at least 500 cSt at 40°C.

Preferably the viscosity ranges from about 200 to 40,000 cSt at 40°C, more preferably from about 500 to 40,000 cSt at 40°C. In another embodiment, the viscosity ranges from about 500 to 5000 cSt at 40°C.

In one of its method aspects, this invention is directed to a method for enhancing the formation of a solid, non-migratory coherent mass at a selected vascular site of a mammal which method comprises:

(a) placing a delivery device having an ejection port at a selected vascular site in a mammal;

(b) delivering through the ejection port of the delivery device a composition comprising a biocompatible polymer, a biocompatible solvent and optionally a contrast agent wherein the viscosity of the composition is at least about 150 cSt at 40°C.

Preferably the composition delivered in (b) above comprises a biocompatible polymer, a biocompatible contrast agent and a biocompatible solvent which solubilizes the biocompatible polymer wherein the weight percents of the biocompatible polymer, contrast agent and biocompatible solvent are based on the total weight of the complete composition; further wherein sufficient amounts of said polymer are employed in said composition such that, upon delivery to a vascular site, a polymer precipitate forms which embolizes said vasculare site; and still further wherein the viscosity of said composition is at least about 150 cSt at 40°C.

More preferably, the composition delivered in (b) above comprises a a biocompatible polymer at a concentration of from about 2 to 50 weight percent, a biocompatible contrast agent at a concentration of from about 10 to about 40 weight percent, and a biocompatible solvent from about 10 to 88 weight percent wherein the weight percent of the biocompatible polymer, contrast agent and biocompatible solvent is based on the total weight of the complete composition and further wherein the composition has a viscosity of at least about 150 and more preferably at least about 200 cSt at 40°C.

Optionally, prior to the delivering aspect of (b) above, blood flow through the vascular site can be attenuated by insertion of a blood flow attenuating device immediately upstream the ejection port. Such a blood flow attenuating device is preferably an inflatable microballoon which permits both normal and attenuated blood flow depending upon whether the microballoon is deflated or inflated.

The contrast agent is either a water soluble contrast agent or a water insoluble contrast agent. Preferably, the water insoluble contrast agent is a biocompatible material selected from the group consisting of barium sulfate, tantalum powder and tantalum oxide.

In still a further preferred embodiment, the biocompatible solvent is dimethylsulfoxide (DMSO), ethanol, ethyl lactate or acetone.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the migration of the precipitate formed in a tube simulating *in vivo* conditions during injection of a composition comprising approximately 8.5 weight percent biocompatible polymer and having a viscosity of approximately 90 cSt at 40°C.

Figure 2 illustrates the migration of the precipitate formed in a tube simulating *in vivo* conditions during injection of a composition comprising approximately 17 weight percent of the same biocompatible polymer as in Figure 1 and having a viscosity of approximately 1100 cSt at 40°C.

DETAILED DESCRIPTION OF THE INVENTION

This invention is directed to novel compositions for embolizing blood vessels which are particularly suited for treating vascular lesions via catheter delivery of the composition.

However, prior to discussing this invention in further detail, the following terms will first be defined:

The term "embolizing" refers to a process wherein a material is injected into a blood vessel which, in the case of, for example, aneurysms, fills or plugs the aneurysm sac and/or encourages clot formation so that blood flow into the aneurysm ceases, in the case of high flow AVM's forms a plug or clot to control/reroute blood flow to permit proper tissue perfusion, and, in the case of a vascular site, fills the vascular site to prevent blood flow there through. Embolization of the blood vessel is, therefore, important in preventing/controlling bleeding due to lesions (e.g., organ bleeding, gastrointestinal bleeding, vascular bleeding as well as bleeding associated with an aneurysm). In

addition, embolization can be used to ablate diseased tissue (e.g., tumors, etc.) by cutting off its blood supply.

The term "biocompatible polymer" refers to polymers which, in the amounts employed, are non-toxic and substantially non-immunogenic when used internally in the patient and which are substantially insoluble in the body fluid of the mammal. The biocompatible polymer can be either biodegradable or, preferably, non-biodegradable.

Biodegradable polymers are disclosed in the art. For example, Dunn, et al.[10] discloses the following examples of biodegradable polymers: linear-chain polymers such as polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers and combinations thereof. Other biodegradable polymers include, for example, gelatin, collagen, etc.

Suitable non-biodegradable biocompatible polymers include, by way of example, cellulose acetates[2,6-7] (including cellulose diacetate[5]), ethylene vinyl alcohol copolymers[4,8], hydrogels (e.g., acrylics), polyacrylonitrile, polyvinylacetate, cellulose acetate butyrate, nitrocellulose, copolymers of urethane/carbonate, copolymers of styrene/maleic acid, and mixtures thereof[9].

Preferably, the biocompatible polymer employed does not cause an adverse inflammatory reaction when employed *in vivo*. The particular biocompatible polymer employed is selected relative to the viscosity of the resulting polymer solution, the solubility of the biocompatible polymer in the biocompatible solvent, and the like. For example, the selected biocompatible polymer should be soluble in the amounts employed in the selected biocompatible solvent and the resulting composition should have a viscosity suitable for *in vivo* delivery by the methods of this invention.

Preferred biocompatible polymers include cellulose diacetate and ethylene vinyl alcohol copolymer. Cellulose diacetate polymers are either

commercially available or can be prepared by art recognized procedures. In a preferred embodiment, the number average molecular weight, as determined by gel permeation chromatography, of the cellulose diacetate composition is from about 25,000 to about 100,000 more preferably from about 50,000 to about 75,000 and still more preferably from about 58,000 to 64,000. The weight average molecular weight of the cellulose diacetate composition, as determined by gel permeation chromatography, is preferably from about 50,000 to 200,000 and more preferably from about 100,000 to about 180,000. As is apparent to one skilled in the art, with all other factors being equal, cellulose diacetate polymers having a lower molecular weight will impart a lower viscosity to the composition as compared to higher molecular weight polymers. Accordingly, adjustment of the viscosity of the composition can be readily achieved by merely adjusting the molecular weight of the polymer composition.

Ethylene vinyl alcohol copolymers comprise residues of both ethylene and vinyl alcohol monomers. Small amounts (e.g., less than 5 mole percent) of additional monomers can be included in the polymer structure or grafted thereon provided such additional monomers do not alter the properties of the composition. Such additional monomers include, by way of example only, maleic anhydride, styrene, propylene, acrylic acid, vinyl acetate and the like.

Ethylene vinyl alcohol copolymers are either commercially available or can be prepared by art recognized procedures. As is apparent to one skilled in the art, with all other facts being equal, copolymers having a lower molecular weight will impart a lower viscosity to the composition as compared to higher molecular weight copolymers. Accordingly, adjustment of the viscosity of the composition as necessary for catheter delivery can be readily achieved by merely adjusting the molecular weight of the copolymer composition.

As is also apparent, the ratio of ethylene to vinyl alcohol in the copolymer affects the overall hydrophobicity/hydrophilicity of the composition which, in turn, affects the relative water solubility/insolubility of the composition as well as the rate of precipitation of the copolymer in an

aqueous environment (e.g., blood or tissue). In a particularly preferred embodiment, the copolymers employed herein comprise a mole percent of ethylene of from about 25 to about 60 and a mole percent of vinyl alcohol of from about 40 to about 75. These compositions provide for requisite precipitation rates suitable for use in the methods described therein.

The term "contrast agent" refers to a biocompatible radiopaque material capable of being monitored during injection into a mammalian subject by, for example, radiography. The contrast agent can be either water soluble or water insoluble.

Examples of water soluble contrast agents include metrizamide, iopamidol, iothalamate sodium, iodomide sodium, and meglumine. Examples of water insoluble contrast agents include tantalum, tantalum oxide, and barium sulfate, each of which is commercially available in the proper form for *in vivo* use including a preferred particle size of about 10 μm or less. Other water insoluble contrast agents include gold, tungsten, and platinum powders.

Preferably, the contrast agent is water insoluble (i.e., has a water solubility of less than 0.01 mg/ml at 20°C).

The term "biocompatible solvent" refers to an organic material liquid at least at body temperature of the mammal in which the biocompatible polymer is soluble and, in the amounts used, is substantially non-toxic. Suitable biocompatible solvents include, by way of example, ethyl lactate, dimethylsulfoxide, analogues/homologues of dimethylsulfoxide, ethanol, acetone, and the like. Aqueous mixtures with the biocompatible solvent can also be employed provided that the amount of water employed is sufficiently small that the dissolved polymer precipitates upon contact with the blood. Preferably, the biocompatible solvent is dimethylsulfoxide.

The term "encapsulation" as used relative to the contrast agent being encapsulated in the polymer precipitate is not meant to infer any physical entrapment of the contrast agent within the precipitate much as a capsule encapsulates a medicament. Rather, this term is used to mean that an integral coherent precipitate forms which does not separate into individual components.

The term "migration distance" refers to the linear (confluent) distance the solid precipitate forms when 0.1 mL of a composition described herein is injected into an optically clear tube using the test method of Example 3 below. In this example, the migration distance is measured along the length of the precipitation formed as illustrated in Figures 1 and 2.

The term "proximate the ejection port" means that the solid coherent mass initially forms at or within about 5 mm of the ejection port. Preferably the solid coherent mass forms within about 3 mm and more preferably within about 1 mm of the ejection port.

Compositions

The polymer compositions employed in this invention are prepared by conventional methods whereby each of the components is added and the resulting composition mixed together until the overall composition is substantially homogeneous.

For example, these compositions can be prepared by adding sufficient amounts of the biocompatible polymer to the biocompatible solvent to achieve the effective concentration for the polymer composition. Preferably, the polymer composition will comprise from about 2 to about 50 weight percent of the biocompatible polymer composition based on the total weight of the polymer composition and more preferably from about 12 to about 50 weight percent. If necessary, gentle heating and stirring can be used to effect dissolution of the biocompatible polymer into the biocompatible solvent, e.g., 12 hours at 50°C for EVOH being dissolved in DMSO.

The viscosity of the composition is controlled either by the amount of polymer employed and/or its molecular weight. For example, high viscosity compositions which employ low concentrations of polymer can be achieved by use of very high molecular weight biocompatible polymers (e.g., average molecular weight greater than 250,000). Such factors are well known in the art. In any event, the compositions described herein have a viscosity of at least about 150 cSt at 40°C and preferably at least about 200 cSt at 40°C.

Sufficient amounts of the contrast agent can be added to the biocompatible solvent to achieve the effective concentration for the complete composition. Preferably, the composition will comprise from about 10 to about 40 weight percent of the contrast agent and more preferably from about 20 to about 40 weight percent and even more preferably about 30 weight percent. Insofar as water insoluble contrast agents are not soluble in the biocompatible solvent, stirring is employed to effect homogeneity of the resulting suspension for compositions employing such constrast agents.

In order to enhance formation of the suspension, the particle size of water insoluble contrast agents is preferably maintained at about 10 μm or less and more preferably at from about 1 to about 5 μm (e.g., an average size of about 2 μm). In one preferred embodiment, the appropriate particle size of the contrast agent is prepared, for example, by fractionation. In such an embodiment, a water insoluble contrast agent such as tantalum having an average particle size of less than about 20 microns is added to an organic liquid such as ethanol (absolute) preferably in a clean environment. Agitation of the resulting suspension followed by settling for approximately 40 seconds permits the larger particles to settle faster. Removal of the upper portion of the organic liquid followed by separation of the liquid from the particles results in a reduction of the particle size which is confirmed under an optical microscope. The process is optionally repeated until a desired average particle size is reached.

The particular order of addition of components to the biocompatible solvent is not critical and stirring of the resulting solution or suspension is conducted as necessary to achieve homogeneity of the composition. Preferably, mixing/stirring of the composition is conducted under an anhydrous atmosphere at ambient pressure. The resulting composition is heat sterilized and then stored preferably in sealed bottles or vials until needed.

Each of the polymers recited herein is commercially available but can also be prepared by methods known in the art. For example, polymers are typically prepared by conventional techniques such as radical, thermal, UV, γ irradiation, or electron beam induced polymerization employing, as necessary,

a polymerization catalyst or initiator to provide for the polymer composition. The specific manner of polymerization is not critical and the polymerization techniques employed do not form a part of this invention.

In order to maintain solubility in the biocompatible solvent, the polymers described herein are preferably not cross-linked.

Methods

The compositions described above can then be employed in methods for the catheter assisted embolization of mammalian blood vessels. In such methods, a sufficient amount of this composition is introduced into the selected blood vessel via a catheter delivery means under fluoroscopy so that upon precipitation of the polymer, the blood vessel is embolized. The particular amount of embolic composition employed is dictated by the total volume of the vasculature to be embolized, the concentration of polymer in the composition, the rate of precipitation (solids formation) of the polymer, etc. Such factors are well within the skill of the art.

One particularly preferred method for catheter delivery of the embolic compositions of this invention to the selected vascular site is via a small diameter medical catheter connected to a threaded syringe. One example of a novel threaded syringe has a threaded plunger which is operable as a conventional syringe for aspiration of the embolic composition and then is used in a threaded manner for delivery of the embolic composition. The threaded syringe may also include a tactile or audible indication of delivery which allows clinician to monitor delivery of the embolic composition without looking at the syringe. The catheter for delivery of the embolic compositions preferably has a burst strength of 100 psi or greater, and more preferably 200 psi or greater, and still more preferably 1000 psi or greater. In order to prevent catheter burst, the threaded syringe may be provided with a force release mechanism which prevents the clinician from applying pressures above the catheter burst strength. As an alternative delivery means to the threaded syringe, a syringe pump may be used.

Preferably, in order to enhance the *in vivo* delivery of a uniform suspension of this composition, the composition is mixed at a temperature of above 40°C which ensures formation of a uniform suspension and then this heated composition is transferred while maintaining its temperature above room temperature and preferably above 40°C into the catheter for *in vivo* delivery.

Specifically, a uniform suspension is achieved by mixing the compositions at a temperature above about 40°C, preferably from above about 40°C to about 90°C, and more preferably from about 50°C to about 70°C. The particular temperature employed should be sufficiently high to ensure adequate mixing of the composition.

In a particularly preferred embodiment, the composition is heated for a period of time from at least about 3 to about 20 minutes and preferably from about 5-10 minutes to facilitate formation of a uniform suspension. In some cases, the formation of a uniform suspension requires that the heated composition be placed in a suitable mixer, e.g., vortex mixer, and is mixed until the suspension is homogeneous. In this case, after formation of the homogenous suspension via the mixer, the composition is preferably reheated to a temperature of from above about 40°C to about 90°C and preferably from about 50°C to about 70°C. The specific temperature employed for heating is selected relative to the biocompatible solvent and biocompatible polymer employed. Such selections are well within the skill of the art.

In either case, the heated composition is then transferred preferably via a syringe and delivered into the catheter under conditions wherein the temperature of the composition is above room temperature and preferably above about 40°C. In one preferred embodiment, the conditions which effect such transfer are rapid transfer (e.g., transfer occurs within 2 minutes of heating cessation) of the composition to the catheter.

Surprisingly, the heated composition maintains both a uniform suspension and ease of delivery during catheter injection into a vascular site in a mammal and, when ejected at the distal end of the catheter, there is no evidence of trauma to this site. See, for example, U.S. Patent Application

Serial No. _____ filed concurrently herewith as Attorney Docket No. 018413-195 and entitled "Methods for Delivering In Vivo Uniform Dispersed Embolic Compositions of High Viscosity" which application is incorporated herein by reference in its entirety.

The particular catheter employed is not critical provided that polymeric catheter components are compatible with the embolic composition (i.e., the catheter components will not readily degrade in the embolic composition). In this regard, it is preferred to use polyethylene in the catheter components because of its inertness in the presence of the embolic composition described herein. Other materials compatible with the embolic compositions can be readily determined by the skilled artisan and include, for example, other polyolefins, fluoropolymers (e.g., Teflon™), silicone, etc.

When delivered by catheter, preferred delivery techniques include those set forth in concurrently filed U.S. Patent Application Serial No. _____, entitled "Methods For Embolizing Vascular Sites With an Embolizing Composition" and assigned Attorney Docket No. 018413-270 which application is incorporated herein by reference in its entirety.

In another embodiment, the catheter employs an interface device which connects to the syringe to create a blunt interface between a DMSO composition not containing either a biocompatible polyer or a contrast agent and the embolic composition described herein. Such devices are disclosed in U.S. Patent Application Serial No. _____, concurrently filed herewith, and entitled "Interface Needle and Method for Creating a Blunt Interface Between Delivered Liquids" as Attorney Docket No. 018413-265 which is incorporated herein by reference in its entirety.

Utility

The compositions described herein are useful in embolizing mammalian blood vessels which, in turn, can be used to prevent/control bleeding (e.g., organ bleeding, gastrointestinal bleeding, vascular bleeding, bleeding associated with an aneurysm), to ablate diseased tissue (e.g., tumors, etc.), and to treat aneurysms and/or AVMs. Accordingly, these compositions

find use in human and other mammalian subjects requiring embolization of blood vessels.

It is contemplated that these compositions can be employed as a carrier for a compatible pharmaceutically active compound wherein this compound is delivered *in vivo* for subsequent release. Such compounds include, by way of example only, antibiotics, anti-inflammatory agents, chemotherapeutic agents, anti-angiogenic agents, and the like.

The following examples are set forth to illustrate the claimed invention and are not to be construed as a limitation thereof.

EXAMPLES

Unless otherwise stated, all temperatures are in degrees Celsius. Also, in these examples and elsewhere, the following abbreviations have the following meanings:

cc	=	cubic centimeters
cSt	=	centistokes
DMSO	=	dimethylsulfoxide
EVOH	=	ethylene vinyl alcohol copolymer
EVOH-1	=	44 mole percent ethylene/56 mole percent vinyl alcohol having a melt index of about 10
EVOH-2	=	44 mole percent ethylene/56 mole percent vinyl alcohol having a melt index of about 1.5
EVOH-3	=	48 mole percent ethylene/52 mole percent vinyl alcohol and a weight average molecular weight (GPC MW) of 136,000
g	=	gram
mL	=	milliliter
mm	=	millimeter
μm	=	micron

Example 1

This example illustrates the effect of polymer concentration on viscosity and the compositions described herein comprise only biocompatible polymer and biocompatible solvent (DMSO). However, the results of this example correlate to the viscosities of compositions further comprising a

water insoluble contrast agent since this agent will not have any significant effect on viscosity.

In this example, the recited polymer was added to DMSO and stirred until homogenous. Heating of the solution was employed as required to effect dissolution. Viscosities are measure at 40°C and are reported in cSt. The results are set forth below (all percents are weight percents based on the polymer and solvent):

Polymer Type/ Grade	Concentration (% polymer)	Viscosity
EVOH-1	10.00	78
EVOH-1	16.00	346
EVOH-2	8.00	55
EVOH-2	10.00	103
EVOH-2	16.00	472
cellulose diacetate (50,000)	12.00	1355
cellulose diacetate (50,000)	8.00	314
cellulose diacetate (30,000)	12.00	176
cellulose diacetate (30,000)	8.00	56

As is apparent, minimal increases in polymer concentration result in very high increases in viscosity.

Example 2

This example illustrates the preparation of compositions of this invention having a high viscosity. Specifically, EVOH polymer compositions were prepared as follows:

Comparative Example A

approximately 8.5 weight % EVOH-3
30 weight % micronized tantalum
approximately 61.6 weight % DMSO
Viscosity = approximately 90 cSt at 40°C

Composition of Example 2

approximately 17.5 weight % EVOH
30 weight % micronized tantalum
approximately 52.5 weight % DMSO
Viscosity = approximately 1100 cSt at 40°C

In each case, after dissolution of the polymer at 50°C in DMSO with stirring, micronized tantalum (average size 3μm) was then added. The resulting composition was heated for about 5 minutes at 70°C then shaken in a vortex mixer for approximately 20 minutes at room temperature to obtain a uniform suspension of the insoluble tantalum in the composition.

Example 3

The purpose of this example is to establish that reduced precipitate migration can be achieved by increasing the viscosity of the polymer composition.

The compositions of Comparative Example A and Example 2 were tested to determine their relative migration distance under approximate *in vivo* conditions. Specifically, two identical silicone (optically clear) tubes each having an approximate 4 mm lumen were constructed and an aqueous solution of saline at 37°C was allowed to flow there through at a flow rate of 130 mL/minute and a pressure of approximately 120/80 mm of Hg. The two tubes are labeled Tube A and Tube 2.

The compositions of Comparative Example A and Example 2 were loaded into 2 separate syringes which were labeled Syringe A and Syringe 2. The 21 French needle of Syringe A was inserted confluently into the lumen of Tube A to provide access into the lumen. Similarly, the 21 French needle of Syringe 2 was inserted confluently into the lumen of Tube 2 to provide access into the lumen. The contents of each syringe (approximately 0.1 mL) were then injected confluently with the saline flow into their respective tubes at an injection rate of about 0.12 cc/minute.

Upon injection, each composition formed a solid precipitate in the tube. The degree of migration of the precipitate formed about 1 minutes after start of injection was visually determined through the optically clear walls of the tube. Photographs of the formed precipitate were taken and are reproduced as Figures 1 and 2 wherein Figure 1 illustrates the migration of the precipitate formed during injection of the composition of Comparative Example A and

Figure 2 illustrates the migration of the precipitate formed during injection of the composition of Example 2.

The results of this example illustrate that the composition of Example 2 forms a more "ball-like" precipitate with significantly less migration under identical flow conditions as compared to the precipitate formed from the composition of Comparative Example A. In fact, the composition of Example 2 migrated approximately 40% of that of the composition of Comparative Example A.

Example 4

The purpose of this example is to further demonstrate that reduced migration of the formed precipitate can be achieved by increasing the viscosity of the composition.

Specifically, in this example, different polymer compositions were prepared as described above using three different biocompatible polymers [i.e., polyvinylacetate (PVAc), cellulose acetate butyrate (CAB), or ethylene vinyl alcohol (EVOH)]. The concentration (in weight percent based on the total weight of the composition) and molecular weight of each of the polymers are as defined below and were employed in a composition comprising 30 weight percent of tantalum and the balance being DMSO. As noted above, at the same concentration, a higher molecular weight polymer imparts a higher viscosity to these compositions than the same polymer having a lower molecular weight. Accordingly, internal comparisons of migration distance between similar polymers of different molecular weight effectively determines the effect of viscosity on the migration of the formed precipitate.

In these tests, each of the compositions were tested for average migration distance (average of four runs) in the manner described in Example 3 above with the exceptions that the 21 French needle of each syringe was used to puncture the wall of tube at an angle of about 30° to provide access into the lumen; the average ejection rate was 0.10 cc/minute and the saline flow rate was 300 mL/min.

The results of this analysis are set forth in Tables I-III below:

Table I

Polymer	MW (weight ave. based on GPC)	Concentration (wght. %)	Viscosity (cSt at 40°C)	Average Migration Distance (in mm)
EVOH	136,360	3	6	28[A]
EVOH	136,360	15	217	18
EVOH	136,360	30	2355	15

Table II

Polymer	MW (weight ave. based on GPC)	Concentration (wght. %)	Viscosity (cSt at 40°C)	Average Migration Distance (in mm)
PVAc	500,000	3	16	38
PVAc	500,000	15	1072	28
PVAc	500,000	30	21284	15
PVAc	83,000	3	4	*
PVAc	83,000	15	41	44
PVAc	83,000	30	242	38
PVAc	12,800	3	2	*
PVAc	12,800	15	6	41[a]
PVAc	12,800	30	16	51[a]

Table III

Polymer	MW (number ave.)	Concentration (wght. %)	Viscosity (cSt at 40°C)	Average Migration Distance (in mm)
CAB	70,000	3	41	23[A]
CAB	70,000	15	7599	16
CAB	70,000	30	[b]	11
CAB	30,000	3	6	*
CAB	30,000	15	155	18
CAB	30,000	30	1288	19
CAB	12,000	3	5	*
CAB	12,000	15	81	25
CAB	12,000	30	601	17

* indicates that the formed precipitate fragmented and did not form a coherent mass.

[A] indicates that these samples fragmented and that the distance of migration is representative

[B] Value not determined

The above data indicates that for viscosities at least about 150 cSt at 40°C and preferably at least about 200 cSt at 40°C, an increase in viscosity correlates with a reduction in migration distance.

The above data further indicates that an increase in concentration of polymer alone without a corresponding increase in viscosity does not provide for reduced migration distances. For example, in Table II, the first and last compositions have approximately equal viscosities but the last composition has a 10 fold higher concentration of polymer. Nevertheless, the latter composition does not reduce the migration distance as compared to the first composition.

Example 5

The purpose of this example is to still further demonstrate that reduced migration of the formed precipitate can be achieved by increasing the viscosity of the composition. The procedures used in this example were similar to those of Example 4.

The results of this test are set forth in Table IV below:

Table IV

Polymer	Concentration (wght. %)	Viscosity (cSt at 40°C)	Average Migration Distance (in mm)[2]	Standard Deviation
EVOH-3	4.6	18	33.2	6.18
EVOH	6.2	34	28.2	4.15
EVOH	9.2	90	24.2	4.92
EVOH	12.3	200	24.6	3.44
EVOH	15.4	500	23.2	2.59
EVOH	23.1	2500	20.0	2.92

From the foregoing description, various modifications and changes in the above described methods will occur to those skilled in the art. All such modifications coming within the scope of the appended claims are intended to be included therein.

WHAT IS CLAIMED IS:

1. A composition comprising:

(a) a biocompatible polymer;

(b) a biocompatible contrast agent; and

(c) a biocompatible solvent which solubilizes said biocompatible polymer

wherein sufficient amounts of said polymer are employed in said composition such that, upon delivery to a vascular site, a polymer precipitate forms which embolizes said vasculare site; and

further wherein the viscosity of said composition is at least about 150 cSt at 40°C.

2. A composition comprising:

(a) a biocompatible polymer at a concentration of from about 2 to 50 weight percent;

(b) a biocompatible contrast agent at a concentration of from about 10 to about 40 weight percent; and

(c) a biocompatible solvent from about 10 to 88 weight percent

wherein the weight percents of the biocompatible polymer, contrast agent and biocompatible solvent are based on the total weight of the complete composition; and

further wherein the composition has a viscosity of at least about 150 cSt at 40°C.

3. The composition according to Claim 1 or Claim 2, wherein said composition has a viscosity of at least about 200 cSt at 40°C.

4. The composition according to Claim 3, wherein said composition has a viscosity of at least about 500 cSt at 40°C.

5. The composition according to Claim 4, wherein said composition has a viscosity of from about 500 to 5,000 cSt at 40°C.

6. The composition according to Claim 1 or Claim 2 wherein said composition has a migration distance of less than 25 mm.

7. The composition according to Claim 1 or Claim 2, wherein the concentration of biocompatible polymer employed in said composition is from 6 to 50 weight percent.

8. The composition according to Claim 7, wherein the concentration of biocompatible polymer employed in said composition is from 8 to 30 weight percent.

9. The composition according to Claim 1 or Claim 2 wherein said biocompatible solvent is selected from the group consisting of ethyl lactate, dimethylsulfoxide, ethanol and acetone.

10. The composition according to Claim 9 wherein said biocompatible solvent is dimethylsulfoxide.

11. The composition according to Claim 1 or Claim 2 wherein said contrast agent is a water insoluble contrast agent.

12. The composition according to Claim 11 wherein said water insoluble contrast agent is selected from the group consisting of tantalum, tantalum oxide, tungsten and barium sulfate.

13. The composition according to Claim 12 wherein said contrast agent is tantalum.

14. The composition according to Claim 1 or Claim 2 wherein said contrast agent is a water soluble contrast agent.

15. The composition according to Claim 1 or Claim 2 wherein said biocompatible polymer is a non-biodegradable, biocompatible polymer.

16. The composition according to Claim 15 wherein said non-biodegradable, biocompatible polymer is selected from the group consisting of cellulose acetates, ethylene vinyl alcohol copolymers, hydrogels, polyacrylonitrile, polyvinylacetate, cellulose acetate butyrate, nitrocellulose, copolymers of urethane/carbonate, copolymers of styrene/maleic acid, and mixtures thereof.

17. The composition according to Claim 16 wherein said biocompatible polymer is an ethylene and vinyl alcohol copolymer.

18. The composition according to Claim 1 or Claim 2 wherein said biocompatible polymer is a biodegradable, biocompatible polymer.

19. A method for enhancing the formation of a solid, non-migratory coherent mass at a selected vascular site of a mammal which method comprises:

(a) placing a delivery device having an ejection port at a selected vascular site in a mammal;

(b) delivering through the ejection port of the delivery device a composition comprising a biocompatible polymer, a biocompatible solvent and optionally a contrast agent wherein the viscosity of the composition is at least about 150 cSt at 40°C.

20. The method according to Claim 19 wherein, prior to (b) above, a blood flow attenuating device is insert immediately upstream the ejection port of said catheter.

21. The method according to Claim 20 wherein said blood flow attenuating device is an inflatable microballoon which permits both normal and attenuated blood flow depending upon whether the microballoon is deflated or inflated.

22. The method according to Claim 19, wherein said composition has a viscosity of at least about 200 cSt at 40°C.

23. The method according to Claim 22, wherein said composition has a viscosity of at least about 500 cSt at 40°C.

24. The method according to Claim 23, wherein said composition has a viscosity of from about 500 to 5,000 cSt at 40°C.

25. The method according to Claim 19 wherein said composition has a migration distance from the point of injection of less than 25 mm.

26. The method according to Claim 19, wherein the concentration of biocompatible polymer employed in said composition is from 6 to 50 weight percent.

27. The method according to Claim 26, wherein the concentration of biocompatible polymer employed in said composition is from 8 to 30 weight percent.

28. The method according to Claim 19 wherein said biocompatible solvent is selected from the group consisting of ethyl lactate, dimethylsulfoxide, ethanol and acetone.

29. The method according to Claim 28 wherein said biocompatible solvent is dimethylsulfoxide.

30. The method according to Claim 19 wherein said contrast agent is a water insoluble contrast agent.

31. The method according to Claim 30 wherein said water insoluble contrast agent is selected from the group consisting of tantalum, tantalum oxide, tungsten and barium sulfate.

32. The method according to Claim 31 wherein said contrast agent is tantalum.

33. The method according to Claim 19 wherein said contrast agent is a water soluble contrast agent.

34. The method according to Claim 19 wherein said biocompatible polymer is a non-biodegradable, biocompatible polymer.

35. The method according to Claim 34 wherein said non-biodegradable, biocompatible polymer is selected from the group consisting of cellulose acetates, ethylene vinyl alcohol copolymers, hydrogels, polyacrylonitrile, polyvinylacetate, cellulose acetate butyrate, nitrocellulose, copolymers of urethane/carbonate, copolymers of styrene/maleic acid, and mixtures thereof.

36. The method according to Claim 35 wherein said biocompatible polymer is an ethylene and vinyl alcohol copolymer.

37. The method according to Claim 19 wherein said biocompatible polymer is a biodegradable, biocompatible polymer.

ABSTRACT OF THE DISCLOSURE

Disclosed are novel compositions for embolizing blood vessels which are particularly suited for treating vascular lesions via catheter delivery.

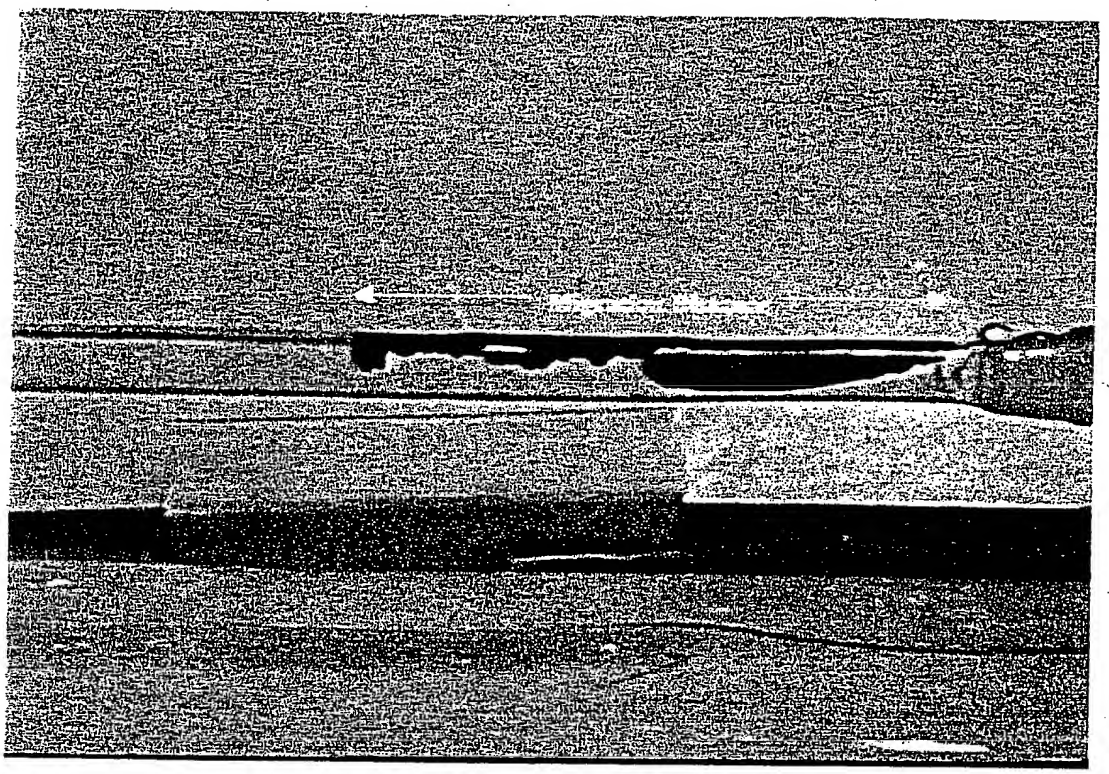

Figure 1

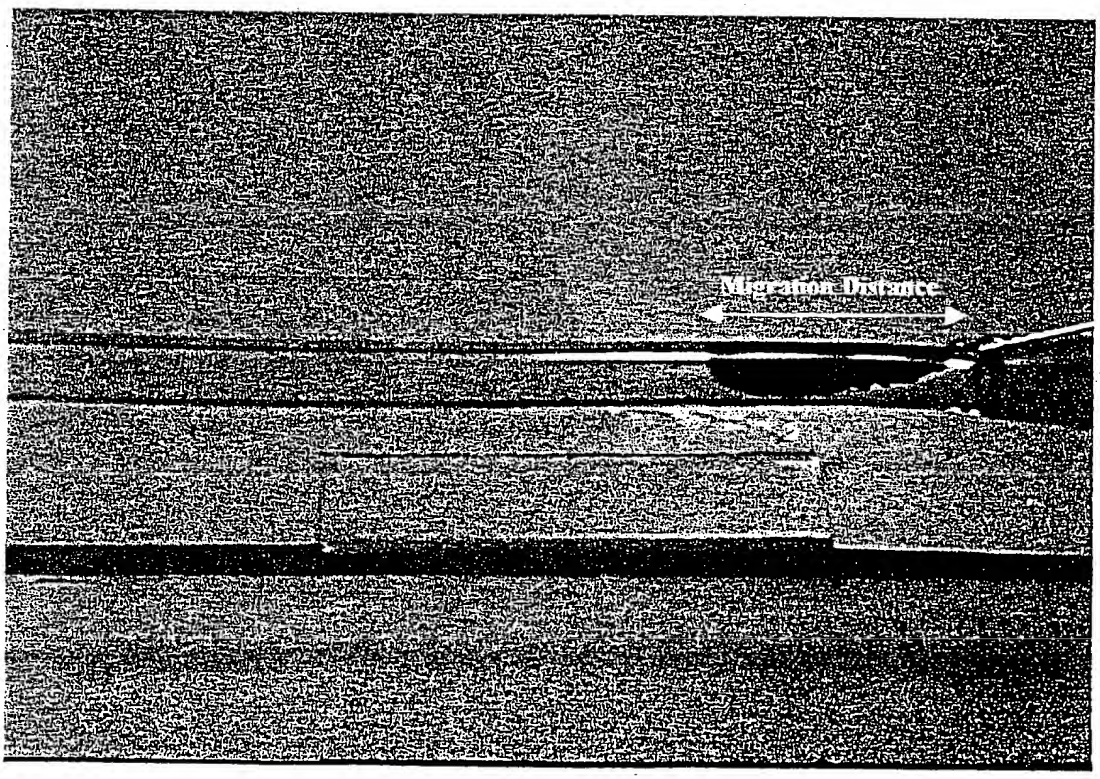

Figure 2

MICRO THERAPEUTICS, INC.

EMPLOYEE CONFIDENTIAL INFORMATION AGREEMENT

In consideration and as a condition of my employment, or continued employment, by MICRO THERAPEUTICS, INC. and/or by companies which it owns, controls, or is affiliated with, or their successors in business (hereafter referred to as "the Company), and the compensation paid therefore:

1. Confidentiality

I agree to keep confidential, except as the Company may otherwise consent in writing, and not to disclose or make any use of except for the benefit of the Company, at any time, either during or subsequent to my employment, any trade secrets, confidential information, knowledge, data or other information of the Company relating to products, processes, know-how, designs, formulas, test data, customer lists, business plans, marketing plans and strategies, pricing strategies or other subject matter pertaining to any business of the Company or any of its clients, customers, consultants, licensees or affiliates, which I may produce, obtain or otherwise acquire during the course of my employment, except as herein provided. I further agree not to deliver, reproduce or in any way allow any such trade secrets, confidential information, knowledge, data or other information, or any documentation relating thereto, to be delivered or used by any third parties without specific direction or consent of a duly authorized representative of the Company.

2. Conflicting Employment/Return of Confidential Material

I agree that during my employment with the Company, I will not engage in any other employment, occupation, consulting or other activity relating to the business in which the Company is now or may hereafter become engaged or which would otherwise conflict with my obligations to the Company. In the event of my termination of employment with the Company for any reason whatsoever, I agree to promptly surrender and deliver to the Company all records, materials, equipment, drawings, documents and data of any nature pertaining to any invention, tradé secret or confidential information of the Company or to my employment, and I will not take with me any description containing or pertaining to any confidential information, knowledge or data of the Company which I may produce or obtain during the course of my employment. In the event of the termination of my employment for any reason whatsoever, I agree to sign and deliver the "Termination Certificate" attached hereto as Exhibit A.

3. Non Solicitation

I agree that during my employment and for the two year period following my employment I will not solicit or induce any employee or consultant of the Company to quit their employment, cease doing business with the Company or accept employment with any entity that I am then involved with, unless I am specifically authorized to do so by the Company. In addition, during my employment and for the two year period following my employment I will not solicit or induce any customer of the Company to cease doing business with the Company.

4. **Assignment of Inventions**

I agree that all computer programs, documentation and other copyrightable materials to which I contribute during my employment shall be considered "works for hire" and shall be the sole property of the Company. I hereby assign and transfer to the Company my entire right, title and interest in and to all inventions (as used in the Agreement, "inventions" shall include but not be limited to ideas, improvements, designs and discoveries) whether or not patentable and whether or not reduced to practice, made or conceived by me (whether made solely by me or jointly with others) during the period of my employment with the Company, which relate in any manner to the actual or demonstrably anticipated business, work or research and development of the Company or its subsidiaries, or result from or are suggested by any task assigned to me or any work performed by me for or on behalf of the Company or its subsidiaries. I agree that all such inventions are the sole property of the Company provided, however, that this Agreement does not require assignment of an invention which qualifies fully for protection under Section 2870 of the California Labor Code (hereafter referred to as "Section 2870"). A copy of Section 2870 is attached as Exhibit B.

5. **Disclosure of Inventions and Patents**

I agree that in connection with any "invention" as defined in Paragraph 3 above:

a) I will disclose such invention promptly in writing to my immediate superior at the Company, with a copy to the president, regardless of whether I believe the invention is protected by Section 2870, in order to permit the Company to claim rights to which it may be entitled under this Agreement. Such disclosure shall be received in confidence by the Company.

b) I will, at the Company's request, promptly execute a written assignment of title to the Company for any invention required to be assigned by Paragraph 3 ("assignable invention") and I will preserve any such assignable invention as confidential information of the Company.

c) Upon request, I agree to assist the Company or its nominee (at its expense) during and at an time subsequent to my employment in every reasonable way to obtain for its own bene patents and copyrights for such assignable inventions in any and all countries, whic inventions shall be and remain the sole and exclusive property of the Company or its nomine whether or not patented or copyrighted. I agree to execute such papers and perform su lawful acts as the Company deems to be necessary to allow it to exercise all right, title a interest in such patents and copyrights.

6. **Execution of Documents**

In connection with Paragraph 4(c), I further agree to execute, acknowledge and deliver to Company or its nominee upon request and at its expense all such documents, including applications patents and copyrights and assignments of inventions, patents and copyrights to be issued therefore the Company may determine necessary or desirable to apply for and obtain letters, patents and copyri on such assignable inventions in any and all countries and/or to protect the interest of the Company c nominee in such inventions, patents and copyrights, and to vest title thereto in the Company c nominee.

7. **Maintenance of Records**

I agree to keep and maintain adequate and current written records of all inventions made by me (in the form of notes, sketches, drawings and as may be specified by the Company), which records shall be available to and remain the sole property of the Company at all times.

8. **Prior Inventions**

It is understood that all inventions if any, patented or unpatented, which I made prior to my employment by the Company are excluded from the scope of this Agreement. To preclude any possible uncertainty, I have set forth on Exhibit C attached hereto a complete list of all my prior inventions, including numbers of all patents and patent applications, and a brief description of all unpatented inventions which are not the property of a previous employer. I represent and covenant that the list is complete and that, if no items are on the list, I have no such prior inventions. I agree to notify the Company in writing before I make any disclosure or perform any work on behalf of the Company which appears to threaten or conflict with proprietary rights I claim in any invention or idea. In the event of my failure to give such notice, I agree that I will make no claim against the Company with respect to any such inventions or ideas.

9. **Other Obligations**

I acknowledge that the Company from time to time may have agreements with other persons or with the U.S. Government or governments of other countries, or agencies thereof, which impose obligations or restrictions on the Company regarding inventions made during the course of work thereunder or regarding the confidential nature of such work. I agree to be bound by all such obligations and restrictions and to take all action necessary to discharge the obligations of the Company thereunder.

10. **Trade Secrets of Others**

I represent that my performance of all the terms of this Agreement and as an employee of the Company does not and will not breach any agreement to keep in confidence proprietary information, knowledge or data acquired by me in confidence or in trust prior to my employment with the Company, and I will not disclose to the Company or induce the Company to use any confidential or proprietary information or material belonging to any previous employer or others. I agree not to enter into any agreement either written or oral in conflict herewith.

11. **Modifications**

This Agreement may not be changed, modified, released, discharged, abandoned or otherwise amended, in whole or in part, except by an instrument in writing, signed by me and the Company. I agree that any subsequent change or changes in my duties, salary, or compensation shall not affect the validity or scope of this Agreement.

12. **Entire Agreement**

I acknowledge receipt of this Agreement and agree that with respect to the subject matter thereof it is my entire agreement with the Company, superseding any previous oral or written communications, representations, understandings or agreements with the Company or any officers or representative thereof.

13. **Severability**

In the event that any paragraph or provision of this Agreement shall be held to be illegal or unenforceable in any jurisdiction, such paragraph or provision shall, as to that jurisdiction, be adjusted and reformed, if possible, in order to achieve the intent of the parties, and if such paragraph or provision cannot be adjusted and reformed, such paragraph or provision shall, for the purposes of that jurisdiction be voided and severed from this Agreement, and the entire Agreement shall not fail on account thereof but shall otherwise remain in full force and effect.

14. **Successors and Assigns**

This Agreement shall be binding upon my heirs, executors, administrators or other legal representative and is for the benefit of the Company, its successors and assigns.

15. **Governing Law**

This Agreement shall be governed by the laws of the location of the Company's corporate headquarters, which is presently located in the State of California; provided, however, that in the event this provision is deemed to be unenforceable by a local judicial authority or governmental agency, then the laws of the location of my employment shall apply.

16. **Counterparts**

This Agreement may be signed in two counterparts, each shall be deemed an original and both of which shall together constitute one agreement.

EMPLOYEE

Chinh N. Tran
(Employee's Signature)

CHINH N. TRAN
(Print Name)

Date: Oct 1st, 1998

MICRO THERAPEUTICS, INC.

By: George Wallace
George Wallace, President

Date: 12/9/98

EXHIBIT A

TERMINATION CERTIFICATE

This is to certify that I do not have in my possession, nor have I failed to return, any records, documents, data, specifications, drawings, blueprints, reproductions, sketches, notes, reports, proposals or copies of them, or other documents or materials, equipment, or other property belonging to the Company, its successors and assigns (hereafter referred to as the "Company").

I further certify that I have complied with and will continue to comply with all the terms of the Employee Proprietary Information Agreement signed by me with the Company, including the reporting of any inventions (as defined therein) conceived or made by me covered by the Agreement.

I further agree that in compliance with the Employee Proprietary and Confidential Information Agreement, I will preserve as confidential all trade secrets, confidential information, knowledge, data, or other information relating to products, processes, know-how, designs, formulas, test data, customer lists, or other subject matter pertaining to any business of the Company or any of its clients, customers, consultants, licensees, or affiliates.

_____

Employee's Signature

_____

Print Name

_____

Date

EXHIBIT B

SECTION 2870
CALIFORNIA LABOR CODE

Any provision in an employment agreement which provides that an employee shall assign or offer to assign any of his or her rights in an invention to his or her employer shall not apply to an invention for which no equipment, supplies, facility, or trade secret information of the employer was used, and which was developed entirely on the employee's own time, and:

a) which does not relate to the business of the employer or to the employer's actual or demonstrably anticipated research or development, or

b) which does not result from any work performed by the employee for the employer.

Any provision which purports to apply to such an invention is to that extent against the public policy of this state and is to that extent void and unenforceable.

EXHIBIT C

LIST OF PRIOR INVENTIONS

Title	Date	Identifying Number or Brief Description